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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,551	12/11/2001	Keith D. Allen	R-227	4290

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DELTAGEN, INC.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,551	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004 and 17 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-35 and 38-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-35 and 38-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/30/04 has been entered.

Claims 33-35 and 38-46 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The Declaration under 37 CFR 1.132 filed 9/17/04 is insufficient to overcome the rejection of claims 33-35 and 38-46 based upon lack of Utility under 35 USC 101 and insufficiency of disclosure under 35 USC 112, first paragraph, for the reasons set forth below.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 33-35 and 38-46 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either an asserted utility which is **specific and substantial,** or a well established utility. **This is a new ground of rejection.**

The invention is drawn to a construct targeting a mouse brain-specific membrane-anchored protein (BSMAP) gene; a method for producing the same targeting construct, a transgenic mouse whose genome comprises a homozygous disruption in the endogenous BSMAP gene, wherein the transgenic mouse exhibits increased prepulsed inhibition relative to a wild-type mouse; as well as a cell or tissue obtained from the same transgenic mouse; a method for making the same transgenic mouse, and methods for identifying an agent that modulates prepulse inhibition and for identifying a potential therapeutic agent for the treatment of schizophrenia using a transgenic mouse comprising a homozygous disruption in endogenous mouse BSMAP gene.

The specification teaches by exemplification the preparation of a transgenic mouse whose genome comprises a homozygous disruption of the BSMAP gene, wherein the transgenic mouse displays **supposedly a significantly increased Prepulsed inhibition**, particularly with a 100 dB prepulse in comparison with the age- and gender matched wild-type control mouse (page 51, lines 29-31). However, upon examination of Figure 3, the only relevant data provided by the instant specification, the observed difference in Prepulsed inhibition between the transgenic mouse comprising a homozygous disruption in the endogenous BSMAP gene and the wild-type control mouse is apparently not significant (please note that the large error bars of the Prepulse inhibition values for the control wild-type mouse extend to and include the mean Prepulse inhibition values for the transgenic knockout mouse). Submission of the Declaration under 37 CFR 1.132 on 9/17/04 only showed that there is indeed a

significant difference in the percent prepulse inhibition for the 120 decibel pulse preceded by a 100 decibel prepulse (PPI100/120) between wild-type and the transgenic mice. Therefore, the only apparent significant difference in the phenotype between a wild-type control mouse and a transgenic mouse comprising a homozygous disruption in the endogenous BSMAP gene is the percent prepulse inhibition for the 120 decibel pulse preceded by a 100 decibel prepulse.

It is noted that the Prepulse inhibition (PPI) test only reflects one component of the startle reflex response, and that impaired PPI is thought to reflect dysfunctional sensorimotor gating mechanism. Moreover, the instant specification teaches specifically that PPI can be modulated by negative affective states like fear or stress (page 51, lines 19-20), and that the homozygous mutant mice have a stimulus processing phenotype opposite to that observed in schizophrenic patients (page 52, lines 1-2), all of which clearly indicate that the homozygous mutant mouse of the instant invention appears to be not an acceptable model of schizophrenia (relevant to claim 46). Furthermore, while it is known that human schizophrenics display PPI deficit, several other distinctly different human disorders are also known to be characterized by PPI deficit, including schizotypal personality disorder, Huntington's disease, DiGeorge/Velocardiofacial syndrome (Geyer et al., Mol. Psychiatry 7:1039-1053, 2002), and that even in 2002 there is still no gene or genes that have been confirmed as "schizophrenia genes". Moreover, PPI responses are also affected by the strains of mice used as well as developmental changes (Geyer et al., page 1040). It appears that the PPI responses are non-specific!

Therefore, it is apparent that PPI responses do not correlate to any specific disease or disorder (e.g., schizophrenia or other neuropsychiatric disorders), let alone for the significant difference in the percent prepulse inhibition for the 120 decibel pulse preceded by a 100 decibel prepulse (PPI100/120) observed between wild-type and the transgenic mice. Additionally, even in 20003 Harrison et al. (Mol. Cell. Neuroscience 24:1170-1179, 2003) still state "Prepulse inhibition (PPI) in animals and man is thought to reflect sensorimotor gating processes" (page 1175, col. 2, last paragraph), and "The underlying changes that occur in behavioural, genetic, or pharmacological models of PPI are poorly understood, not least because the associated circuitry is complex and is thought to include serial and parallel inputs from frontal areas into a pontine startle ciruit" (page 1176, col. 1, middle of the paragraph). Thus, it is apparent that the transgenic mouse comprising a homozygous disruption in the endogenous BSMAP gene that differs from a wild-type mouse in the percent prepulse inhibition for the 120 decibel pulse preceded by a 100 decibel prepulse does not have a specific and substantial utility at the effective filing date of the present application (12/13/2000).

At the effective filing date of the present application, little was known about the physiological role or function of the BSMAP gene. Elson et al. (Biochem. Biophys. Res. Commun. 264:55-62, 1999; IDS) have identified the BSMAP gene to be localized on human chromosome 19p12, and speculate that due its highly preferential expression in the brain the BSMAP may have a role in brain function. Elson et al. further state "We failed to identify any genetic disease implicating CNS function which have been mapped to this precise region of chromosome 19." (page 55, col. 2, second last sentence).

Because the defined function for the BSMAP or its gene is not known and is not taught in the specification, coupled with the lack of a correlation between the PPI100/120 response to any specific disease or disorder or a specific physiological condition, the invention therefore has no utility which is **specific** and **substantial** at the effective filing date of the present application. The speculation that BSMAP may play a generic role in brain function or its gene disruption is somehow associated with schizophrenia is not deemed to be a specific and substantial utility for the presently claimed invention. Nor is the use of the disclosed transgenic mouse in studies of sensorimotor gating to understand the role of genes in regulating PPI (This requires further studies or researches) is deemed to be a substantial utility.

The specification asserts a variety of utilities for the claimed invention, including uses of the cell-and animal-based systems of the present invention as models for diseases, for identifying compounds that ameliorate disease symptoms, for production of antibodies, for identifying agents that modulate the expression or the function of the BSMAP gene. However, such uses would require the determination of the physiological function or role of the BSMAP gene and its gene product, and in the absence of such guidance provided by the instant specification and in the prior art, they do not constitute a substantial utility at the effective filing date of the present application. A substantial utility is a utility that defines a "real world" use. Utilities which require further research to identify or confirm a real world use are not substantial utilities.

For the reasons set forth above, a skilled artisan would not be able to use the presently claimed invention for any substantial purpose without further research and experimentation.

Response to Arguments

Applicant's arguments related in part to the above rejection in the Amendment filed 8/30/04 (pages 6-7) have been fully considered, but they are not found persuasive.

1. Applicant argues that the transgenic mouse represents the ultimate model of antagonism of the target BSMAP gene, and that mutant knockout transgenic mice with single gene disruptions represent a powerful tool to study sensorimotor gating and to identify and characterize putative and known therapeutic agents capable of affecting prepulse inhibition, as well as to determine or confirm the mechanism of action of therapeutic agents used in the treatment of sensorimotor gating related diseases such as schizophrenia. Applicant further argues that the issues of negative states such as fear or stress do not apply to the utility of the claimed transgenic mouse because the increased PPI phenotype is only observed in the homozygous knockout mice.

Firstly, the only apparent difference in the phenotype between a wild-type control mouse and a transgenic mouse comprising a homozygous disruption in the endogenous BSMAP gene is an increased prepulse inhibition for the 120 decibel pulse preceded by a 100 decibel prepulse observed in the transgenic mouse. This phenotypic difference does not correlate to any specific disease or disorder or any specific physiological condition. Even several years after the effective filing date of the present application

Harrison et al. (Mol. Cell. Neuroscience 24:1170-1179, 2003) still note that Prepulse inhibition (PPI) in animals and man **is thought to reflect** sensorimotor gating processes, and that the underlying changes that occur in behavioural, genetic, or pharmacological models of PPI **are poorly understood**. Additionally, Geyer et al. (Molecular Psychiatry 7:1039-1053, 2002) state "[v]arious inbred mouse strains and genetically modified mouse lines have been examined **to investigate the potential genetic basis** of sensorimotor gating", and "The use of mice to study PPI is increasing at a dramatic rate and is helping **to increase our understanding of the biological basis for sensorimotor gating**" (see abstract). All of these indicate that at the effective filing date of the present application, the transgenic mouse of the presently claimed invention does not have a specific and substantial utility. Please note that a substantial utility is a utility that defines a "real world" use. Utilities which require further research or further investigation to identify or confirm a real world use are not substantial utilities.

Secondly, the PPI responses are apparently affected by a whole host of unrelated factors such as stress, fear, genetic background of the mice used, the developmental stage, a variety of mutations including the homozygous disruption of the BSMAP (non-specific responses!), and the apparent lack of a correlation between an increased in PPI100/120 response to any specific disease or disorder or a specific physiological condition. Therefore, it is unclear about the biological significance of any agent that is capable of modulating the PPI using the transgenic mouse of the present invention, let alone whether it has any therapeutic effects on the treatment of

sensorimotor gating related diseases such as schizophrenia. Once again, utilities which require further research or further investigation to identify or confirm a real world use are not substantial utilities.

Thirdly, nothing was known about the physiological role or function of the BSMAP gene at the effective filing date of the present application, and that Elson et al. (Biochem. Biophys. Res. Commun. 264:55-62, 1999; IDS) also state "We failed to identify any genetic disease implicating CNS function which have been mapped to this precise region of chromosome 19" (page 55, col. 2, second last sentence) in reference to the location of human BSMAP on human chromosome 19p12.

2. Applicant argues that the utility of the claimed mouse relates to the prepulse inhibition phenotype, and that the evidence supporting a link between PPI deficits and multiple human disorders only supports the value of the transgenic mouse in discovering the role of the BSMAP gene in such disorders and developing treatments for them by modulating PPI.

Please note that observed increase in PPI100/120 response for the transgenic mouse relative to the wild-type mouse does not correlate with any specific disease or disorder as already explained above. There is also no evidence in the prior art at the effective filing date of the present application or in the present disclosure that the BSMAP gene has been implicated or involved in any disease or disorder as evidenced by the teachings of Elson et al.

3. Applicant argues that Applicant's disclosure provides evidence of a role for the BSMAP gene in sensorimotor gating, and particularly in prepulse inhibition, and that the lack of a schizophrenia gene is irrelevant for the utility of the claimed transgenic mouse. Applicants further argue that the asserted utility is for screening for agents that affect or modulate a phenotype, such as prepulse inhibition, and the transgenic mouse needs only exhibit the phenotype. A potential therapeutic agent will usually only target one gene or gene product, regardless of whether the symptom or disorder is associated with multiple genes or whether no genes have been identified or linked to the symptom or disorder.

Please note that even in 2003, Prepulse inhibition (PPI) in animals and man **is thought to reflect** sensorimotor gating processes, and that the underlying changes that occur in behavioural, genetic, or pharmacological models of PPI **are poorly understood**, let alone an increase in the PPI100/120 response for the transgenic mouse is a clear indication that the BSMAP gene has a role in sensorimotor gating, not mentioning that the PPI responses are apparently affected by a whole host of unrelated factors such as stress, fear, genetic background of the mice used, the developmental stage (non-specific responses!). Then how can any agent that modulates a prepulse inhibition in the homozygous mutant mouse of the present invention be reasonably expected to be a potential therapeutic agent for the treatment of any disease or disorder, let alone for schizophrenia?

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-35 and 38-46 are rejected under 35 U.S.C. 112, first paragraph. Because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above under 35 U.S.C. 101, one skilled in the art would not know how to use the claimed invention at the effective filing date of the present application.

The specification is not enabled for the present claimed invention for the following reasons.

(1) The breadth of the claims. The instant claims are drawn to a construct targeting a mouse brain-specific membrane-anchored protein (BSMAP) gene; a method for producing the same targeting construct, a murine embryonic stem cell transformed with the same targeting construct, a transgenic mouse whose genome comprises a homozygous disruption in the endogenous BSMAP gene, wherein the transgenic mouse exhibits increased prepulsed inhibition relative to a wild-type mouse, as well as a cell or tissue obtained from the same transgenic mouse, a method for making the same transgenic mouse, and methods for identifying an agent that modulates prepulse inhibition and for identifying a potential therapeutic agent for the treatment of schizophrenia using a transgenic mouse comprising a homozygous disruption in endogenous mouse BSMAP gene.

(2) The state and unpredictability of the prior art. At the effective filing date of the present application, Elson et al. (Biochem. Biophys. Res. Commun. 264:55-62, 1999; IDS) have identified the BSMAP gene to be localized on human chromosome 19p12, and speculate that due its highly preferential expression in the brain the BSMAP may have a role in brain function. Elson et al. further state "We failed to identify any genetic disease implicating CNS function which have been mapped to this precise region of chromosome 19." (page 55, col. 2, second last sentence). In effect, little was known about the physiological role or function for BSMAP gene and its gene product. Additionally, even several years after the effective filing date of the present application (12/13/2000), there is still no gene or genes that have been confirmed as "schizophrenia genes". While it is known that human schizophrenics display PPI deficit, several other distinctly different human disorders are also known to be characterized by PPI deficit, including schizotypal personality disorder, Huntington's disease, DiGeorge/Velocardiofacial syndrome, PPI responses are also affected by the strains of mice used as well as developmental changes and emotional states such as stress and fear (Geyer et al., Mol. Psychiatry 7:1039-1053, 2002). Thus, it appears that the PPI responses are non-specific! Furthermore, even in 2003 Harrison et al. (Mol. Cell. Neuroscience 24:1170-1179, 2003) still state "Prepulse inhibition (PPI) in animals and man is thought to reflect sensorimotor gating processes" (page 1175, col. 2, last paragraph), and "The underlying changes that occur in behavioural, genetic, or pharmacological models of PPI are poorly understood, not least because the associated

circuitry is complex and is thought to include serial and parallel inputs from frontal areas into a pontine startle ciruit" (page 1176, col. 1, middle of the paragraph).

(3) The amount of direction or guidance provided. Apart from the disclosure of a transgenic mouse whose genome comprises a homozygous disruption of the BSMAP gene, exhibiting a significant increase in the percent prepulse inhibition for the 120 decibel pulse preceded by a 100 decibel prepulse (PPI100/120) relative to an age and gender matched wild-type mouse (see Figure 3 and The 1.132 Declaration filed on 9/17/04), the specification fails to provide sufficient guidance for a skilled artisan on how to use such a homozygous mutant mice. Nor does the instant specification teach that the transgenic mouse display any other phenotypes related to an increased prepulse inhibition. It is further noted that there is no apparent difference in the percent prepulse inhibition for the 120 decibel pulse or 110 decibel pulse preceded by a 85 decibel prepulse or a 90 decibel prepulse, respectively between the transgenic mouse and the wild-type control mouse (See Figure 3). Nor is there an apparent difference in the percent prepulse inhibition for the 120 decibel pulse preceded by either a 80 decibel prepulse or a 90 decibel prepulse between the transgenic mouse and the wild-type control mouse (See Figure 3). This significant increase in the percent prepulse inhibition for the 120 decibel pulse preceded by a 100 decibel prepulse (PPI100/120) response observed for the transgenic mouse apparently does not correlate to any specific disease or disorder or any specific physiological condition. Additionally, the exact physiological role or function of the BSMAP gene itself at the effective filing date of the present application was unknown as evidenced by the teachings of Elson et al. It

is further noted that the PPI responses are affected by a whole host of unrelated factors such as stress, fear, genetic background of the mice used, the developmental stage, a variety of mutations including the homozygous disruption of the BSMAP (non-specific responses!). Thus, how can any agent that modulates a prepulse inhibition in the homozygous mutant mouse of the present invention be reasonably expected to be a potential therapeutic agent for the treatment of any disease or disorder, let alone for schizophrenia?

Given the overall state of the prior art as discussed above, coupled with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and **use** the presently claimed invention.

Similarly, it is would have required undue experimentation for a skilled artisan on how to use a cell or tissue obtained from the transgenic mouse of the presently claimed invention.

As enablement requires the specification to teach how to make and **use** the claimed invention, given the lack of sufficient guidance provided by the present application and in light of the state of the relevant prior art as discussed above, it would have required undue experimentation for a skilled artisan to make and **use** the instant claimed invention.

Response to Arguments

Applicant relies on the same arguments in response to the utility rejection under 35 U.S.C. 101 and the Declaration under 37 CFR 1.132 filed on 9/17/04 for overcoming the rejection under 35 U.S.C. 112, First Paragraph.

Applicant's arguments in response to the utility rejection and the Declaration under 37 CFR 1.132 filed on 9/17/04 are not found persuasive for the reasons already set forth in the above Response to Arguments. Additionally, Examiner maintains that based on the analysis of the Wands factors set forth above, an ordinary skilled artisan would still not know how **to use** the presently claimed invention without undue experimentation.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636; Central Fax No. (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER